

# Estimating the number of tissue resident macrophages

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## Abstract

I provide a simple estimation for the number of macrophages in a tissue, arising from the hypothesis that they should keep infections below a certain threshold, above which neutrophils are recruited from blood circulation. The estimation reads  $N_m = aN_{cel}^\alpha/N_{max}$ , where  $a$  is a numerical coefficient, the exponent  $\alpha \approx 2/3$ , and  $N_{max}$  is the maximal number of pathogens a macrophage may engulf in the time interval,  $t_r$ , between pathogen replications.

Tissue resident macrophages are a subject under intense research by the scientific community [1]. The estimation of their numbers in different tissues is a key problem in the understanding of how the immune system works just after pathogens arrive to a given tissue. A serious effort in determining the average number of all cells of the immune system has already been initiated [2]. In my opinion, the only drawback of such an effort is that there is no idea of what numbers one should expect.

In the present paper, I use very simple reasonings in order to obtain an estimation for the number of resident macrophages in a tissue with  $N_{cel}$  cells.

I start by considering the free evolution of pathogens (bacteria, for example) in a tissue. In the initial instants, the number of pathogens follows an exponential law:

$$N_p = N_p(0) 2^{t/t_r} = N_p(0) \exp(t \ln(2)/t_r), \quad (1)$$

where  $N_p(0)$  is the number at  $t = 0$ , and  $t_r$  is the replication time. The latter is of the order of one hour for bacteria [3].

The exponential growth is, however, constrained by geometry. At later times, the pathogen cluster becomes compact, and only bacteria at the surface may divide, as shown in Fig. 1. The number of new pathogens in a time interval  $t_r$  is, thus, proportional to the cluster surface:

$$\Delta N_p \approx a' N_p^{2/3}. \quad (2)$$

Indeed, the cluster radius is  $R \sim N_p^{1/3}$ , and its surface  $R^2 \sim N_p^{2/3}$ .

With regard to macrophages, I assume that they are uniformly distributed in the tissue, and exhibit high motility. As  $t_r$  is large enough, if the bacterial cluster grows above certain limits, in a time interval of about 3 or 4  $t_r$  most of macrophages can be mobilized to the site of infection. Immunity in a tissue requires that the number of new pathogens, Eq. (2), should be lower than those destroyed by macrophages. The latter is  $N'_m N_{max}$ , where  $N'_m$  is the number of macrophages that have already arrived to the site of infection, and  $N_{max}$  is the maximal number of pathogens that a macrophage may engulf in the time interval  $t_r$ . Thus:

$$a' N_p^{2/3} < N'_m N_{max} < N_m N_{max}, \quad (3)$$

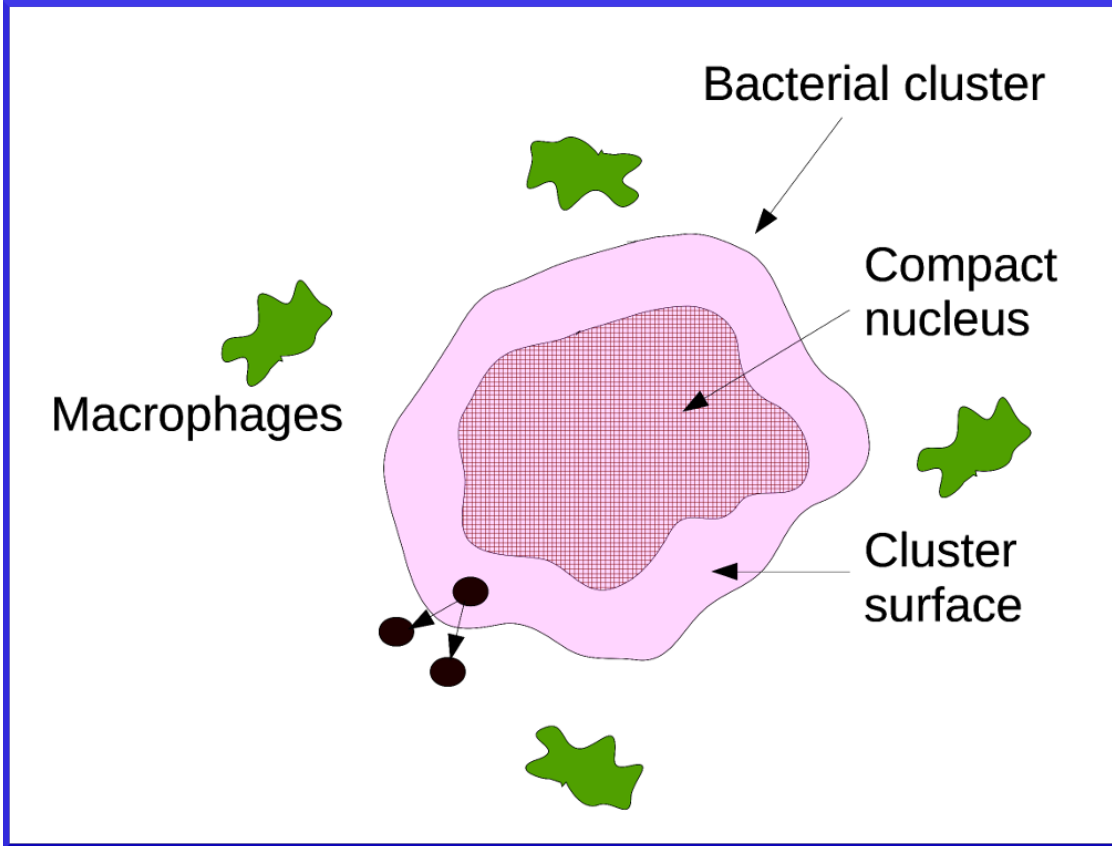


FIG. 1. Evolution of a bacterial cluster at later stages, when only bacteria in the surface have enough space to undergo mitosis. The cluster is surrounded by macrophages.

where  $N_m$  is the number of macrophages in the tissue.

Our final expression for  $N_m$  comes from the idea of a threshold for  $N_p$ , above which neutrophils are called to help fighting the infection. The number of injured cells is naturally related to  $N_p$ . And these injured cells should not overcome a fraction of the number of cells in the tissue (let's say, one hundredth of them, for example). Then, we can write  $N_{cel}$  instead of  $N_p$  in Eq. (3), and introduce a new coefficient  $a$ , instead of  $a'$ , arriving to:

$$N_m > \frac{aN_{cel}^\alpha}{N_{max}}. \quad (4)$$

This is the main result of the paper. The exponent following from Eq. (3) is  $\alpha = 2/3$ , but I have written it more generally in order to consider the effect of different tissue effective dimensionality. With regard to  $N_{max}$ , I guess that it takes similar values for all of the tissues. In around one hour time, a single macrophage in the hyper-activated state may destroy 50

or even a larger number of bacteria [4], for example.

A schematic of what I expect is represented in Fig. 2 for the tissues analyzed in Ref [5]. For simplicity, they are labelled by the organ in which they reside. I rewrite Eq. (4) as  $\log(N_m) > \alpha \log(N_{cel}) + \log(a/N_{max})$ . In a log-log plot of  $N_m$  vs  $N_{cel}$ , I expect a set of tissues to be grouped along a line with slope  $\alpha \approx 2/3$  (a red line in Fig. 2). These are the “normal” tissues [5]. The coefficient  $a$  is very similar for all of them. This coefficient is related to the threshold fraction of tissue that is allowed to be injured by the pathogens.

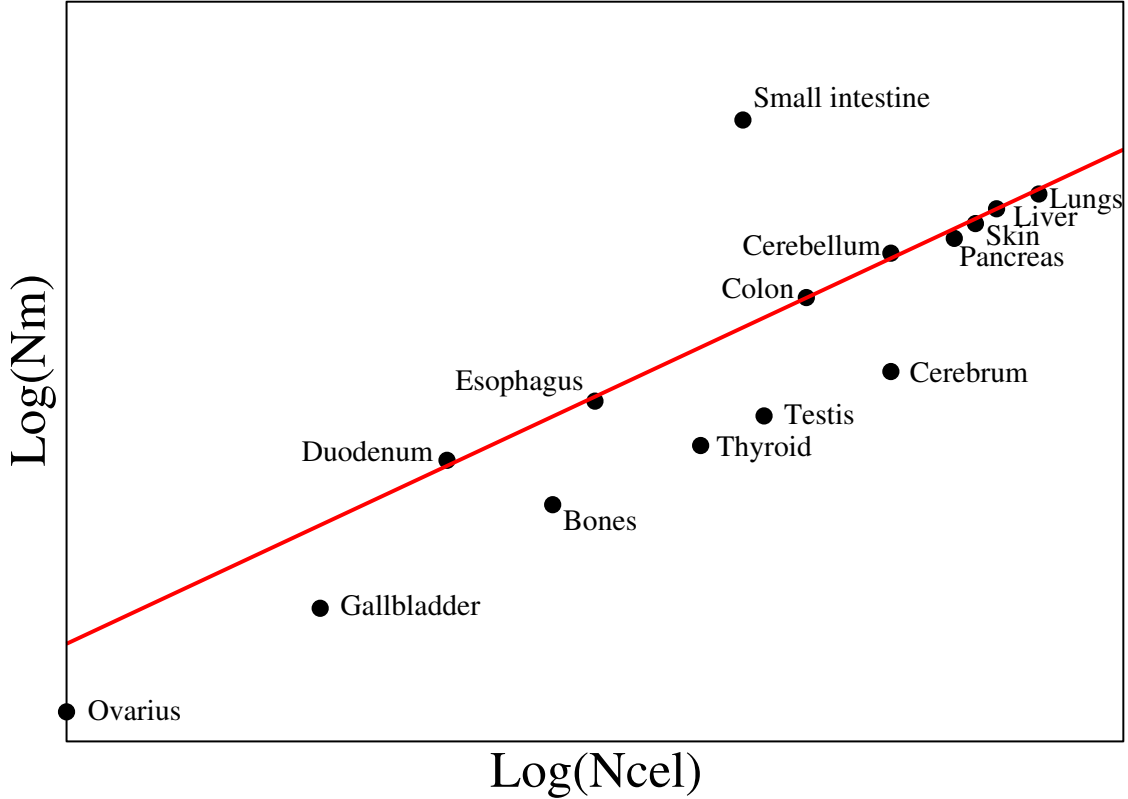


FIG. 2. Schematics of  $\log(N_m)$  vs  $\log(N_{cel})$  in tissues.

Precisely due to lower values of  $a$ , tissues with “reduced” (or privileged) immune protection are located below the line of normal tissues. This reduction in the number of macrophages is compensated by physical barriers (cerebrum, testis) or by physiological conditions (high ph of bile in the gallbladder), for example.

On the other hand, I expect at least one tissue well above the line: the small intestine. This time not  $a$ , but what is higher than normal is the average number of pathogens arriving to the distal end of the small bowel [5]. Eq. (4) gives a lower bound for  $N_m$ . In the small

intestine,  $N_m$  should be much larger than its lower bound in order to protect the tissue against pathogen overload.

In conclusion, I suggest that the number of macrophages resident in a tissue is proportional to  $N_{cel}^\alpha$ , where  $\alpha \approx 2/3$ . A group of tissues should follow this law (the normal tissues). In addition, there should be a second group located below the line of normal tissues, and at least one tissue, the small intestine, above that line. The hypothesis can be tested in the near future.

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